

INTERNATIONAL MONTREUX CONFERENCE OF CHRONOPHARMACOLOGY  
(U) TEXAS UNIV AT HOUSTON SCHOOL OF PUBLIC HEALTH  
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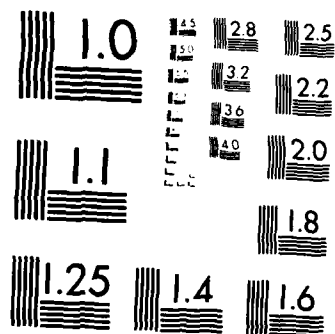
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CONCLUDING REPORT FOR U.S. NAVY CONTRACT

N00014-84-G-0003, PROJECT TITLE:

INTERNATIONAL MONTREUX CONFERENCE OF CHRONOPHARMACOLOGY

Submitted by

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## PREFACE

The contract N00014-84-G-003, entitled First International Montreux Conference of Chronopharmacology, awarded by the United States Navy, essentially supported the organization of the First Montreux International Congress of Chronopharmacology (March 26-30, 1984, Montreux, Switzerland) and provided travel, registration and/or lodging scholarships to United States scientists selected to present papers. According to the terms of the contract, the Principal Investigator agreed to provide 5 copies of the published proceedings--the complete manuscripts from all the participants. The published proceedings of the First Montreux International Congress of Chronopharmacology, edited by Alain Reinberg (Department of Physiologie, Fondation Rotschild, Paris, France), Michael Smolensky (the Principal Investigator) and Gaston Labrecque (School of Pharmacy, Université de Laval, Quebec, Canada), were published as Volume 1 of the Annual Review of Chronopharmacology by Pergamon Press, Oxford, England,

The report which follows is divided into the following three sections: (1) overview summary of the First Montreux International Congress of Chronopharmacology, (2) listing of the participants supported by this contract and (3) 5 copies of the proceedings as stipulated by the contract.

## OVERVIEW SUMMARY OF THE FIRST MONTREUX CONFERENCE

Over the years the number of conferences devoted to the now rapidly growing field of chronopharmacology has been limited. One of the first was held in Velizy, France, as a Satellite Symposium of the 7th International Congress of Pharmacology, July 16-21, 1978. The evaluation of this meeting revealed the necessity for scientists conducting research on biological rhythms and medications to have their own forum to exchange ideas and to report

findings since conferences devoted either to biological rhythms or to pharmacology alone did not satisfactorily meet the requirements either of chronobiologists or pharmacologists concerned with chronopharmacology. The Montreux International Conferences on Biological Rhythms and Medications represent the consequence of the continued growth of interest and research in chronopharmacology. These conferences are intended to provide a forum for scientists, practitioners and industrialists to meet together on a regular basis to exchange ideas and report new findings. At the 1978 meeting in Velizy, there were 80 attendees; at the First Montreux Conference held March 26-30, 1984, there were more than twice that number. At this Montreux meeting, sanctioned both by the International Union of Pharmacology (IUPHAR) and the International Society for Chronobiology, scientists from 16 different countries participated.

One of the major objectives of the Montreux conferences is to promote dialogue, collaboration and friendship among scientists. To ensure this, the choice of the location for these meetings was a critical concern. The Swiss city of Montreux was selected for many reasons. The convention facilities are excellent and the hotels and restaurants are located within walking distance of the meeting site. The relative smallness of Montreux coupled with the favorable atmosphere produced the effect we desire. A European site (Montreux) has been selected since the greatest number of scientists working in this new field is located in the nearby countries. Another major objective of these conferences is to ensure that the scientific merit of each report is high and that the findings be communicated clearly. This former objective has been met first by requiring each submitted abstract to be peer reviewed for scientific merit; the latter was met by organizing the communications so each consists of an oral as well as a poster presentation.

Papers delivered at the First Montreux Conference dealt with 8 major themes as outlined below; with the chairpersons of each indicated in parentheses:

- Section 1. Neurobiology; A. Wirz-Justice (Basel, Switzerland) and W. Rietveld (Leiden, Netherlands)
- Section 2. Antihistamines and Bronchodilators; M. Smolensky (Houston, Texas, USA) and A. Reinberg (Paris, France)
- Section 3. Anticancerous Medications; L.E. Scheving (Little Rock, Arkansas, USA) and E. Haus (Saint-Paul, Minnesota, USA)
- Section 4. Statistics, Methods and Instrumentation, including Pumps; J. DePrins (Brussels, Belgium) and W. Hrushesky (Minneapolis, Minnesota, USA)
- Section 5. Endocrinology and Reproduction; I. Assenmacher (Montellier, France) and Y. Touitou (Paris, France)
- Section 6. Metabolism and Nutrition; H. Nakagawa (Osaka, Japan) and A. Angeli (Torino, Italy)
- Section 7. Cardiovascular and Antiinflammatory Agents; B. Lemmer (Frankfurt/M. West Germany) and G. Labrecque (Quebec, Canada)
- Section 8. Toxicology and Miscellaneous; Aspects of Chronotherapeutics; M. Knapp (Nottingham, U.K.) and I. Ashkenazi (Tel Aviv, Israel)

The rapidity of progress in chronopharmacology has been remarkable considering research in this field dates back such a short time. The provided Proceedings document significant advances in the chronopharmacology of certain classes of medications. This is the case, for example, for: (1)

theophylline (a bronchodilator) with 7 papers dealing with chronokinetics or chronodynamics; (2) antihistamines with 3 papers dealing with chronoeffectiveness; and (3) non-steroid anti-inflammatory medications with 5 papers dealing with either chronopharmacologic or chronotherapeutic aspects. This is the case also for medications used in neurobiology, psychiatry, oncology and cardiology, for which many papers are included. In other fields of medicine a critical mass of information is just being achieved. Research involving biological rhythms and medications requires special considerations; thus, several manuscripts are concerned with statistical techniques of time series data analysis.

Advances in the chronopharmacology of certain types of medications, such as those used for cancer, diabetes and allergy, have been so rapid that chronotherapeutic trials are now ongoing. In the case of the chronotherapy (the administration of medications using chronopharmacologic findings and principles to enhance desired results while minimizing side effects) of cancer, chronopharmacologists eagerly await the development of reliable technology, such as specially designed programmable pumps, to deliver medicines at unequal dosages over time in order to take advantage of the chronotolerances of potent medicines which have rather narrow therapeutic "windows." It is anticipated that a feature of the next Montreux chronopharmacology conference will be the reporting of major advances in medical technology enabling the timely delivery of medical treatments to achieve a chronopharmacologic advantage over equal-dosage, equal-interval treatment schedules which are based on homeostatic concerns only. Anticipated also at the next Montreux conference are reports of findings from now ongoing research studies involving the chronotherapy of hundreds of patients suffering from arthritis and allergy.

TABLE 1

Name of Participant	Academic Affiliation	Title of Presentation
S.G. Special	University of Texas at Dallas Medical School	Chronopharmacological alterations in pentobarbital induced hypnosis and body temperature produced by drugs influencing brain monoamines.
B. Kleiser	Student, University of Minnesota	Quantitative chronopharmacodynamic endpoint in health and schizophrenia: timing of plasma dehydroepiandrosterone (DHEA) vs DHEA-sulfate.
S. Samaan	Florida A&M University School of Pharmacy	Comparison of nocturnal and diurnal theophylline levels at steady state.
W. Kramer	University of Houston School of Pharmacology	Circadian rhythms in steady-state theophylline pharmacokinetics in children.
P.H. Scott	University of Indiana Department of Pediatrics, Pulmonary Medicine	The effect of sustained release theophylline on the circadian variation of pulmonary function in pediatric asthmatic patients.
L.E. Scheving	University of Arkansas Medical School, Department of Anatomy	Meal scheduling, fasting, cellular rhythms and chemotherapy of cancer.
G. Fernandes	University of Texas at San Antonio Medical School, Department of Immunology	The effect of circadian rhythm on immune function and splenic lymphocyte subset ratios in mice.



TABLE 1 (continued)

Name of Participant	Academic Affiliation	Title of Presentation
C. Cornelissen	University of Minnesota Medical School, Department of Pathology	Automatic detection of multiple outliers in physiologic time series: notably temperature.
R.B. Harrist	University of Texas at Houston School of Public Health	An experimental design for evaluating treatment effects and circadian rhythm in respiratory function.
B.P. Hsi	University of Texas at Houston School of Public Health	Rhythmometry analysis on personal computers for applications to chronopharmacology studies.
R.J. Reiter	University of Texas at San Antonio Medical School, Department of Anatomy	Pineal rhythms: modification by drugs and light.
N.H. Rubin	University of Texas at Galveston Medical School, Department of Oncology/Hematology	Apparent absence of influence of melatonin on the circadian rhythm of cell division.
E. Haus	University of Minnesota Medical School, Department of Pathology	Observations on the pharmacokinetics of ethanol.
R.W. Morris	University of Illinois, Chicago, School of Pharmacy	Circatrigintan and circannual angina crises and isosorbide dinitrate compliance rhythms.

TABLE 1 (continued)

Name of Participant	Academic Affiliation	Title of Presentation
J. Fisch and A. Yonovitz	University of Texas at Houston, School of Public Health	Effects of circadian rhythm on kanamycin induced hearing loss.
F. Halberg	University of Minnesota Medical School, Department of Pathology	Circadian and circaseptan aspects of malarial infection and cyclosporine treatment in mice.
J.V. Bruckner	University of Georgia, Athens, Department of Toxicology	Influence of time of exposure to carbon tetrachloride on toxic liver injury.
G. Labrecque	University of Laval, School of Pharmacology	Biological rhythm studies on the hypotensive action of prostaglandin E <sub>2</sub> and arachidonic acid in the rat.
R. Feuers	Ph.D. Student, University of Arkansas	Circadian dependent effect of epidermal growth factor, insulin and glucagon on hepatic pyruvate kinase and malic enzyme of mice.
M.H. Smolensky	University of Texas at Houston, School of Public Health	Introductory speech: The chronopharmacology of bronchodilators for allergic asthma.

#### PARTICIPANTS SUPPORTED BY U.S. NAVY CONTRACT

Table 1 lists the participants who received monetary stipends to attend the First Montreux International Conference of Chronopharmacology. Listed as well is the title of each of their presentations and the institution from which they came.

#### PROCEEDINGS

The Proceedings of the First Montreux International Conference of Biological Rhythms and Medications are contained in Volume One of the Annual Review of Chronopharmacology printed by Pergamon Press, Oxford, England. The Proceedings of subsequent Montreux Conferences, which will be held during the month of March during even-numbered years (the next being March 10-14, 1986) , will be published in future volumes of this Journal. The volumes published in the intervening years will contain in-depth invited contributions by noted scientists dealing with topics relevant to chronopharmacology. In satisfaction of the contract, 5 copies are enclosed with this final report.

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